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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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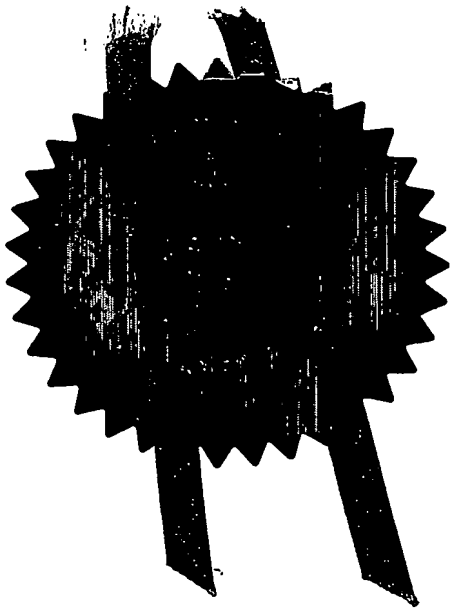

Signed Authorised.

Dated 6 August 2003

Patents Form 1/77

Patents Act 1977
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The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

175EP02 E748632-1 D02029
P01/7700 0.00-0221455.9

1. Your reference — DMW/NM/P33108

2. Patent application number
(The Patent Office will fill in his part) — 0221455.9 | 16 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

5020645 7002

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	57
Claim(s)	0
Abstract	0
Drawings	0

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	P23/77

11. We request the grant of a patent on the basis of this application

Signature _____ Date 16-Sep-02

D M Waters

12. Name and daytime telephone number of person to contact in the United Kingdom: D M Waters 01279 644283

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

COMPOUNDS

The present invention relates to pyrazolopyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolopyridine compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma or allergic rhinitis.

US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

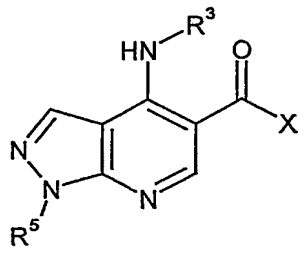
US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic gents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate is known (ethyl 1-ethyl-4-n-butylamino-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate). J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives and their affinities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A1-adenosine receptor ligands.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

The present invention provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



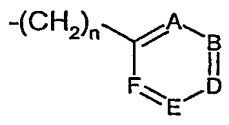
(I)

wherein:

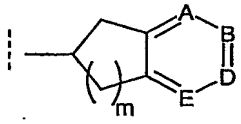
X is NR^1R^2 or OR^{2a}, in which:

R^1 is hydrogen, C_{1-2}alkyl or C_{1-2}fluoroalkyl, and

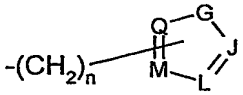
R^2 is hydrogen, C_{1-8}alkyl, C_{1-8} fluoroalkyl, or C_{3-8}cycloalkyl, phenyl optionally substituted with one or two of: a halogen atom, C_{1-2}alkyl, trifluoromethyl, C_{1-2}alkoxy or trifluoromethoxy; or R^2 has the sub-formula (x), (y) or (z):



(x)



(y)



(z)

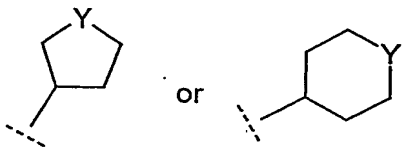
wherein in sub-formula (x) and (z), n = 1 or 2; and in sub-formula (y), m = 1 or 2;

wherein in sub-formula (x) and (y), none, one or two of A, B, D, E and F are nitrogen; and the remaining of A, B, D, E and F are CH or CR^6 where R^6 is a halogen atom, C_{1-4}alkyl, C_{1-4}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, C_{1-2}alkylsulphonyl (C_{1-2}alkyl-SO_2-), C_{1-2}alkyl-SO_2-NH-, R^7R^8N-SO_2-, R^7R^8N-CO-, R^7R^8N, OH, C_{1-4}alkoxymethyl, or C_{1-2}alkyl-SO_2-CH_2-, wherein R^7 and R^8 are independently hydrogen or C_{1-2}alkyl;

wherein in sub-formula (z), G is O or S or NR^9 wherein R^9 is C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one or two of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are CH or CR^6 where R^6 is as defined herein;

or R^1 and R^2 taken together are $-(CH_2)_p-$ where p = 3, 4 or 5 (preferably p = 4);

R^{2a} is C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl; phenyl optionally substituted with one or two of: a halogen atom, C_{1-2}alkyl, trifluoromethyl, C_{1-2}alkoxy or trifluoromethoxy; or R^{2a} has the sub-formula (x), (y) or (z) as defined herein;

R^3 is C_{3-8}cycloalkyl or a heterocyclic group being  in which Y is O, S, SO_2, or NR^{10}; where R^{10} is hydrogen, C_{1-4}alkyl, C_{1-2}fluoroalkyl, C(O)-C_{1-2}alkyl, or C(O)-CF_3;

and wherein in R^3 the C_{3-8}cycloalkyl or heterocyclic group is optionally substituted with one or two substituents being OH, C_{1-2}alkoxy, trimethoxy, or C_{1-2}alkyl group; and wherein any OH, alkoxy or trimethoxy substituent is not substituted at the ring carbon attached to the -NH- group of formula (I) and is not substituted at either ring carbon bonded to the Y group of the heterocyclic group; and

R^5 = hydrogen, C_{1-4}alkyl, C_{1-2}fluoroalkyl, phenyl or benzyl.

Preferably, where X is OR^{2a}, the compound is other than the compound wherein R^5 is methyl, X is OEt, and R^3 is cyclopentyl.

In compounds, for example in the compounds of formula (I), an "alkyl" group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 2-ethylbutan-1-yl, and the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8}cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl , that is contains a 3-6 membered or 5-6 membered carbocyclic ring.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, etc. "Fluoroalkoxy" includes trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom present in compounds, for example in the compounds of formula (I), may be fluorine, chlorine, bromine or iodine.

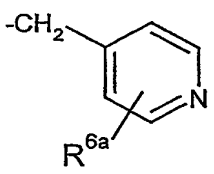
Preferably, X is NR^1R^2.

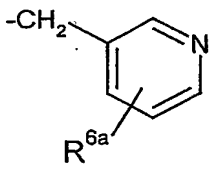
When or R^2 has the sub-formula (x) or (y) or (z), preferably R^2 has the sub-formula (x) or (y), more preferably (x).

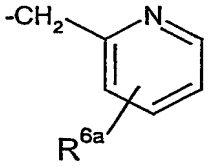
In sub-formula (x) and/or (y), it is preferred that none, one or two of A, B, D, E and F are nitrogen; none, one, two or three of A, B, D, E and F are CR^6; and the remaining of A, B, D, E and F are CH. More preferably, none, one or two of A, B, D, E and F are nitrogen; none or one of A, B, D, E and F are CR^6; and the remaining of A, B, D, E and F are CH.

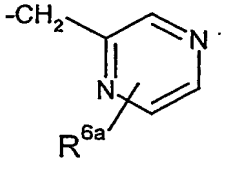
In sub-formula (x) and/or (y), preferably, none or one of A, B, D, E and F are nitrogen, and/or preferably none of A, B, D, E and F are CR^6.

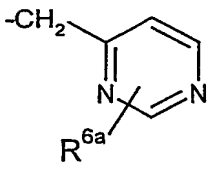
Preferably, sub-formula (x) is: benzyl; phenethyl (Ph-C_2H_4-); benzyl or phenethyl being substituted on the phenyl ring with a single R^6 substituent, or one of the following:

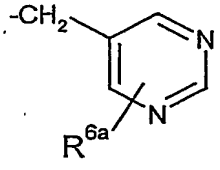




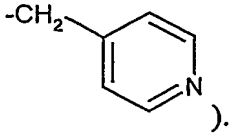




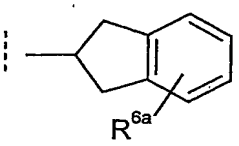




, wherein R^{6a} is either R^6 as defined herein or (preferably) hydrogen.

Most preferably, sub-formula (x) is benzyl or pyridin-4-ylmethyl (i.e. 

).

Preferably, sub-formula (y) is:  , wherein R^{6a} is either R^6 as defined herein or preferably hydrogen.

In sub-formula (x), (y) and (z), preferably, R^6 is a fluorine or chlorine atom, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, methyl-SO_2-NH-, Me_2N-SO_2-, -$CONH_2$, -CONHMe, NMe_2, t-butoxymethyl, or methyl-SO_2-CH_2-. More preferably, R^6 is a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy, methyl-SO_2-NH-, Me_2N-SO_2- or -$CONH_2$.

In sub-formula (x) and/or (y), preferably, any R^6 substituent is present only in B, D and/or E, so that in sub-formula (x) any R^6 substituent is present only in the meta- (3-) and/or para- (4-) positions with respect to the $-(CH_2)_n-$ side-chain.

Overall for R^2, it is preferable that R^2 is hydrogen, C_{1-6}alkyl (e.g. C_{3-6}alkyl), C_{1-4}fluoroalkyl, C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl), phenyl optionally substituted with one of: a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy or trifluoromethoxy; or R^2 has the sub-formula (x), (y) or (z), for example as described above; or R^1 and R^2 taken together are $-(CH_2)_p-$ where p = 4 or 5.

Still more preferably, R^2 is hydrogen, methyl, ethyl, n-propyl, iso-propyl, 2-ethylbutan-1-yl, cyclopentyl, cyclohexyl, fluorophenyl e.g. 4-fluorophenyl, benzyl, or pyridin-4-ylmethyl; or R^1 and R^2 taken together are $-(CH_2)_p-$ where p = 4. Most preferably, R^2 is benzyl, pyridin-4-ylmethyl, or 4-fluorophenyl.

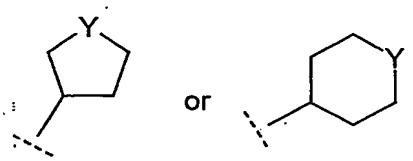
(Similar preferances apply for R^{2a} as for R^2, except that R^{2a} cannot be hydrogen. Most preferably, R^{2a} is ethyl.)

Preferably, R^1 is hydrogen.

Preferably, R^5 is C_{1-4}alkyl or C_{1-2}fluoroalkyl; more preferably C_{1-4}alkyl; still more preferably methyl or ethyl; most preferably ethyl.

Preferably, where R^3 is C_{3-8}cycloalkyl, it is not C_5cycloalkyl, i.e. not cyclopentyl. More preferably, where R^3 is C_{3-8}cycloalkyl, it is C_6cycloalkyl (i.e. cyclohexyl) optionally substituted with one or two substituents being OH, C_{1-2}alkoxy, trimethoxy, or C_{1-2}alkyl group, and wherein any OH, alkoxy or trimethoxy substituent is not substituted at the R^3

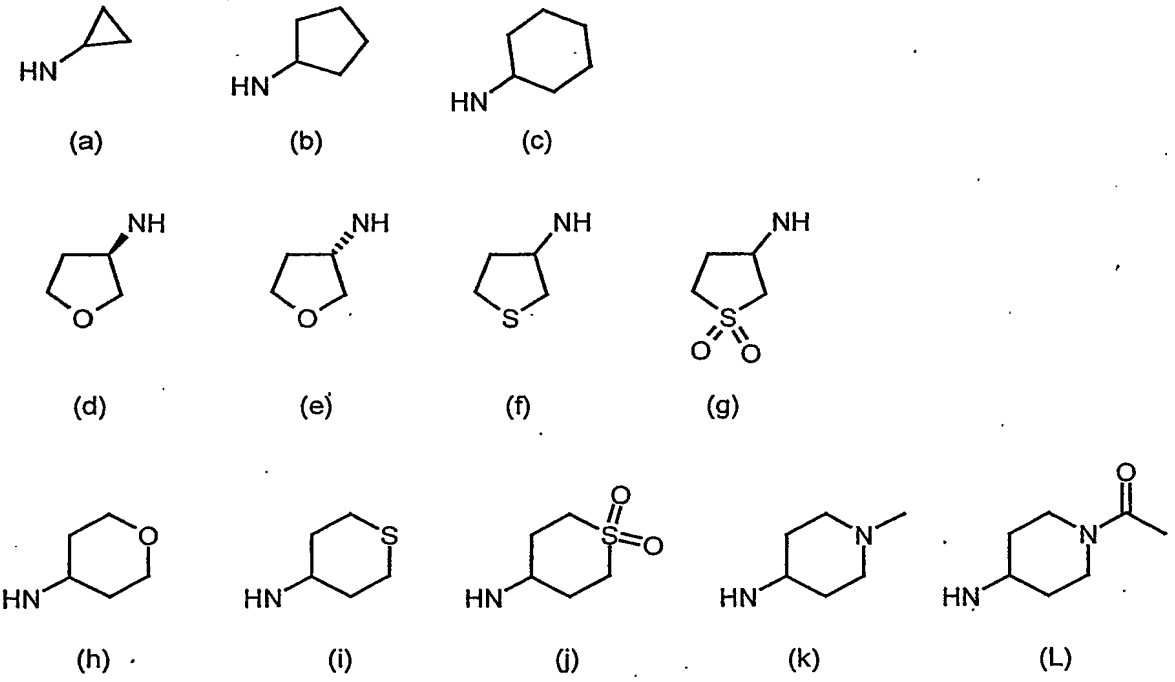
ring carbon attached to the -NH- group of formula (I). Where R^3 is C_{3-8}cyclohexyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted).



Where R^3 is the heterocyclic group being , then preferably Y is O, S, SO_2, NMe or N-C(O)methyl.

Preferably, in R^3 the C_{3-8}cycloalkyl or heterocyclic group is unsubstituted.

Preferably, NHR^3 is of sub-formula (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), or (L):



Most preferably, R^3 is tetrahydro-2H-pyran-4-yl; that is NHR^3 is most preferably of sub-formula (h), shown above.

It is most preferred that the compound of formula (I) or the salt thereof is:

Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,

Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
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N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
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1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
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4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
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N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

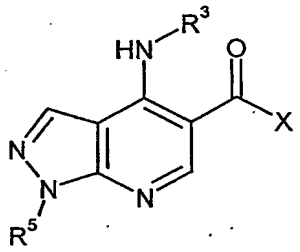
N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, or
4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

Synthetic Process Routes

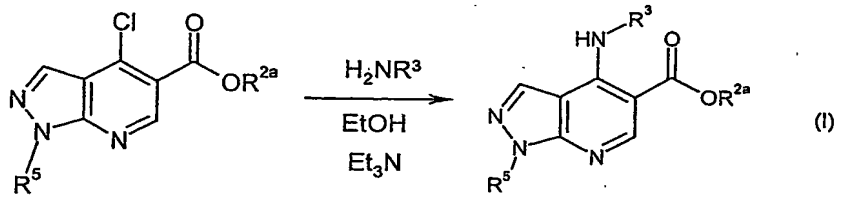
The following processes can be used to make the compounds of the invention:



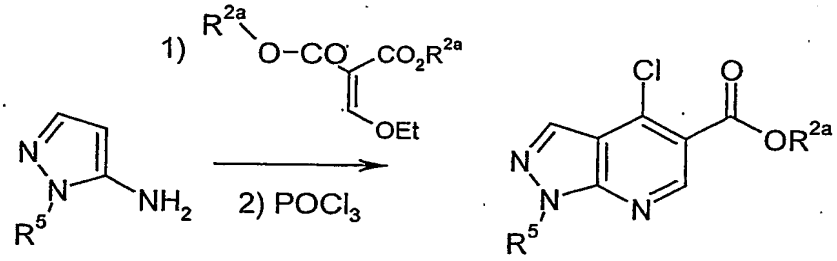
(I)

Process A

Compounds of formula (I) where X = OR^{2a}, can be prepared according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (II) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100 °C , for example ca. 80-90 °C:



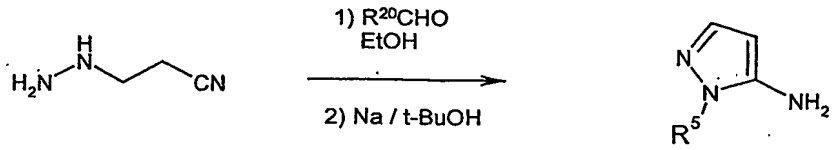
Compounds of formula (II) are also described in the above reference and can be prepared by reaction of a compound of formula (III) with, for example, diethylethoxymethylene malonate (where R^{2a} = Et) with heating, followed by reaction with phosphorous oxychloride, again with heating:



Formula III

Formula II

Where the desired amino pyrazole of formula (III) is not commercially available (for example $R^5 = CH_2Ph$), preparation can be achieved using methods described by Dorgan et. al. in J. Chem. Soc., Perkin Trans. 1, (4), 938-42; 1980, by reaction of cyanoethylhydrazine with a suitable aldehyde of formula $R^{20}CHO$ in a solvent such as ethanol, with heating, followed by reduction with, for example sodium in a solvent such as t-butanol. R^{20} should be chosen so as to contain one less carbon atom than R^5, for example R^{20} = methyl will afford R^5 = ethyl.

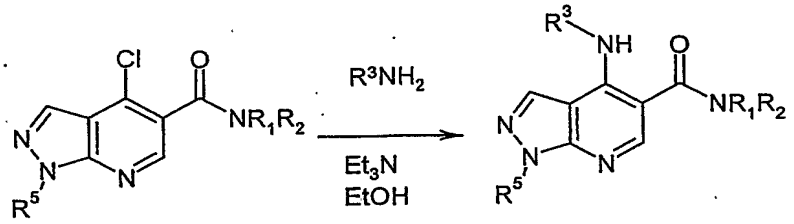


Formula III

Process B

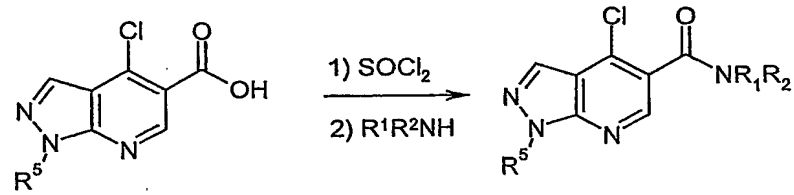
Compounds of formula (I) where $X = NR^1R^2$, can be prepared by reaction of a compound of formula (IV) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction

may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



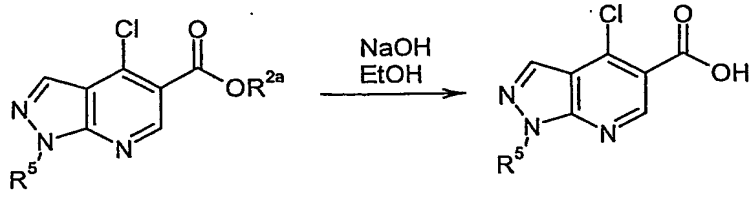
Formula IV Formula I

Compounds of formula (IV) can be prepared in a two step procedure as described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573. This process involves, first, reaction of a compound of formula (V) with thionyl chloride (or another agent suitable for forming an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed intermediate may or may not be isolated. Step two involves reaction with an amine of formula R^1R^2NH, in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethyl amine:



Formula V Formula IV

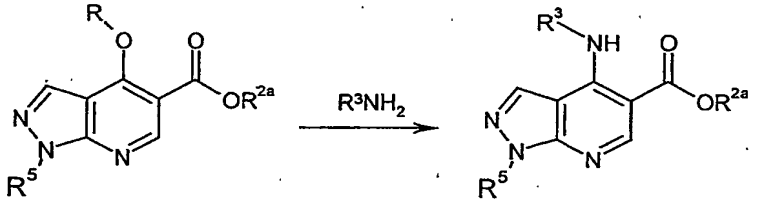
Compounds of formula (V) can be prepared by hydrolysis of an ester of formula (II) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane:



Formula II Formula V

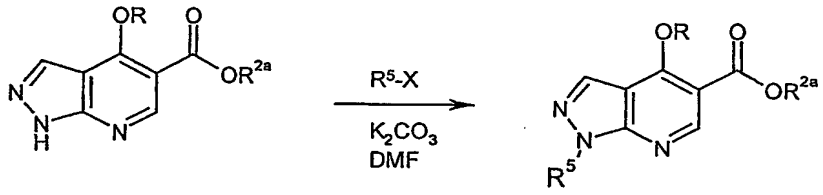
Process C

Compounds of formula (I) can also be prepared according to the method described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573, which involves reaction of a compound of formula (VI), in which -O-R is -O-C_{1-4}alkyl, in particular -O-Et, with an amine of formula R^3NH_2. The reaction may be carried out with or without solvent and may require heating.



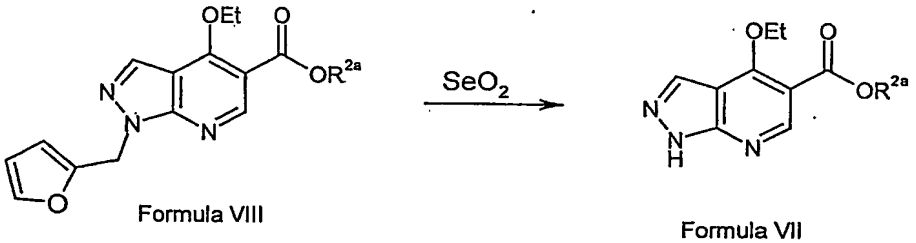
Formula VI Formula I

Compounds of formula (VI) (also described in the above reference) can be prepared by reaction of a compound of formula (VII) with a suitable alkylating agent of formula R^5-X, where X is a leaving group such as halogen. The reaction should be carried out in the presence of a base such as potassium carbonate, in an anhydrous solvent such as DMF:



Formula VII Formula VI

The preparation of compounds of formula VII by oxidative cleavage of compounds of formula VIII is described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573 (further referred to Zuleski et. al. in J. Drug. Metab. Dispos., 1985, 13,139).



Formula VIII Formula VII

Process D:

To form a compound of formula (I) wherein X = NR^1R^2, a compound of formula (I) but wherein X = OH (a carboxylic acid) can be converted into an activated compound of formula (I) but wherein X = a leaving group substitutable by an amine; and subsequently the activated compound can be reacted with an amine of formula R^3NH_2. For example,

the activiated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein X = Cl. This can be formed from the carboxylic acid (X = OH) e.g. by thionyl chloride. See for example Examples 81-85.

The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof, comprising :

(a) for a compound of formula (I) wherein X = OR^{2a}, reaction of a compound of formula (II) with an amine of formula R^3NH_2, or

(b) for a compound of formula (I) wherein X = NR^1R^2, reaction of a compound of formula (IV) with an amine of formula R^3NH_2, or

(c) reaction of a compound of formula (VI), in which -O-R is -O-C_{1-4}alkyl, with an amine of formula R^3NH_2;

(d) to form a compound of formula (I) wherein X = NR^1R^2, conversion of a compound of formula (I) but wherein X = OH (a carboxylic acid) into an activated compound of formula (I) but wherein X = a leaving group substitutable by an amine (preferably, the activiated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein X = Cl), and subsequent reaction of the activated compound with an amine of formula R^3NH_2;

and optionally converting the compound of formula (I) into a salt e.g. a pharmaceutically acceptable salt.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, or multiple sclerosis.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein) and COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (SL Wolda, 2000).

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a

human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-

heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Preferably, a pharmaceutical composition for inhaled administration is incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable on demand and the dose administered by inhalation via the device such as the DISKUS TM device, marketed by GlaxoSmithKline.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg; more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.01 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Biological Test Methods

PDE 3, PDE 4B, PDE 5 Primary assay methods

The activity of the compounds can be measured in the shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5.

Human recombinant PDE4B

Human recombinant PDE4B is disclosed in WO 94/20079 and also M.M. McLaughlin et al., A low *Km*, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA, *J. Biol. Chem.*, 1993, **268**, 6470-6476). Human recombinant PDE4B was expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62. 100,000 x *g* supernatant fractions of yeast cell lysates were used for PDE4B assays and inhibitor studies.

Inhibition of PDE 3, PDE 4B, or PDE 5 activity

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant), PDE3 (from bovine aorta) or PDE5 (human recombinant) was determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so that no more than 20% hydrolysis of the substrate occurred in control wells without compound, during the incubation. For PDE3 and PDE4B assay [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.559) was added to give 0.05uCi per well and ~ 10nM final concentration. For PDE5 assay [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.392) was added to give 0.05uCi per well and ~ 36nM final concentration. Plates were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 1hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited) Results were expressed as pIC_{50} values.

Biological Data obtained for some of the Examples (PDE4B inhibitory activity) is as follows:

Example	PDE4B pIC_{50}
2	7.99
3	7.97
11	7.41
21	8.33
22	7.85
32	7.75

Emesis: Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention causes only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

DCM	dichloromethane
EtOAc	ethyl acetate
Et_2O	diethyl ether
DMF	dimethyl formamide
MeOH	methanol
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance
LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBT	hydroxybenzotriazole
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
DIPEA	diisopropylethyl amine
THF	Tetrahydrofuran
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide

Machine Methods used herein:

<u>LCMS (liquid chromatography/mass spectroscopy)</u>

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS

Flow Rate : 3ml/min
Injection Volume : 5µl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

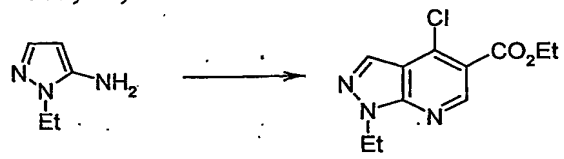
Table of Intermediates

Inter-mediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
4	Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
6	1-Acetyl-4-aminopiperidine
7	1-Methyl-4-aminopiperidine
8	4-Aminotetrahydropyran
8A	Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride
9	(R)-(+)-3-Amino tetrahydrofuran 4-toluene sulphonate
10	(S)-(-)-3-Amino tetrahydrofuran 4-toluene sulphonate
11	Tetrahydro-2H-thiopyran-4-amine
12	Tetrahydro-3-thiopheneamine
13	Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride
14	Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

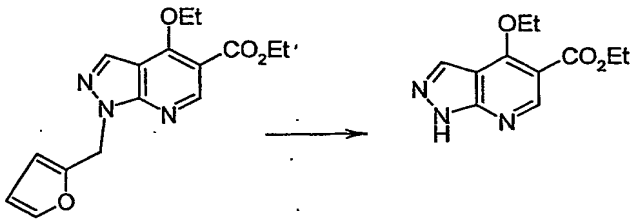
15	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
16	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
17	N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
18	4-Chloro-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
19	4-Chloro-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
20	4-Chloro-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
21	4-Chloro-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridine
22	4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
23	4-Chloro-1-ethyl-N-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
24	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
25	Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
26	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
27	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
28	N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
29	4-Chloro-1-methyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
30	4-Chloro-1-methyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
31	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
32	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
33	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
34	Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
35	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
36	Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
37	Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
38	Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
39	Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
40	Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
41	1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
42	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
43	1-Ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

44	1-Ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
45	4-(Cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
46	4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
47	4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

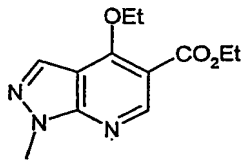
Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:



Intermediate 2: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Prepared by oxidative cleavage (SeO_2) of 1-furanmethyl derivative, as described by T. M. Bare *et. al.* In *J. Med. Chem.*, 1989, 32, 2561-2573, (further referenced to Zuleski, F. R., Kirkland, K. R., Melgar, M. D.; Malbica, *J. Drug. Metab. Dispos.*, 1985, 13, 139)



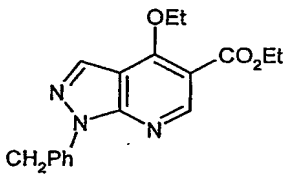
Intermediate 3: Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous dimethylformamide (DMF) (4ml) was treated with iodomethane (0.26ml) and stirred vigorously for 3h. The mixture was then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between dichloromethane (DCM) (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The

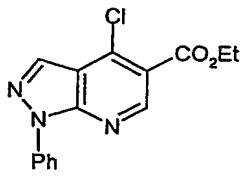
combined organic extracts were dried over anhydrous sodium sulphate and evaporated to an orange solid which was applied to an SPE cartridge (silica, 20g). The cartridge was eluted sequentially with EtOAc : petrol (1:4, 1:2 and 1:1), then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 3 (0.165g). LCMS showed MH^+= 250; T_{RET} = 2.59 min.

Intermediate 4: Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous DMF (4ml) was treated with benzyl bromide (0.72g) then stirred vigorously and heated at 55°C for 4.5h. The mixture was allowed to cool, then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between DCM (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to a yellow oily solid which was dissolved in DCM and applied to an SPE cartridge (silica, 20g). The cartridge was eluted with a gradient of EtOAc : petrol (1:44, 1:2 and 1:1) then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 4 (0.33g). LCMS showed MH^+= 326; T_{RET} = 3.24 min.

Intermediate 5: Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

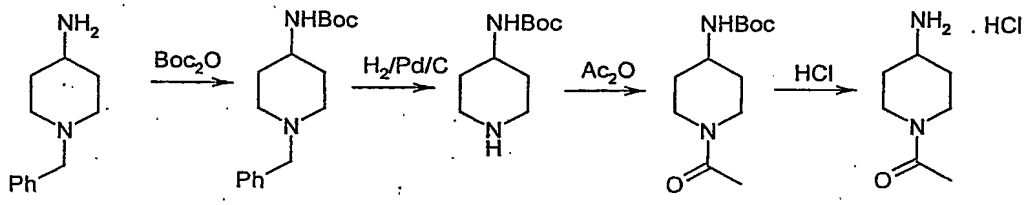


A mixture of 5-amino-1-phenyl pyrazole (2.0g) and diethylethoxymethylene malonate (2.54ml) was heated under Dean Stark conditions at 120°C for 16h. The solution was cooled, phosphorus oxychloride (16ml) was then added and the mixture heated under reflux for a further 20h. Excess phosphorus oxychloride was removed in vacuo and the residue partitioned between diethyl ether and water, proceeding with extreme caution on addition of water. The ethereal layer was washed with further water, then dried over magnesium sulphate and concentrated in vacuo to afford ethyl 4-ethoxy-1-phenyl-1H-

pyrazolo[3,4-b]pyridine-5-carboxylate (2.09g). LCMS showed MH^+= 302; T_{RET} = 3.80 min.

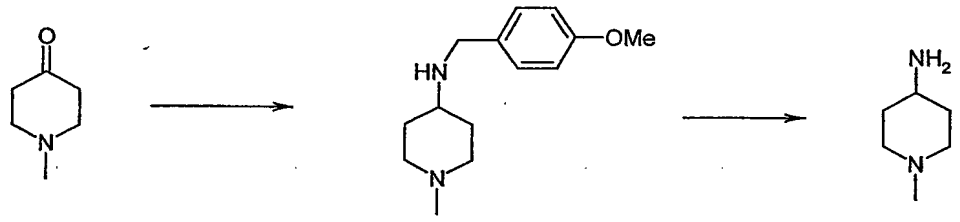
Intermediate 6: 1-Acetyl-4-aminopiperidine

Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:



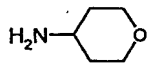
Intermediate 7: 1-Methyl-4-aminopiperidine

Prepared from commercially available N-methyl-4-piperidone as described by C. M. Andersson *et. al.* in WO01/66521:

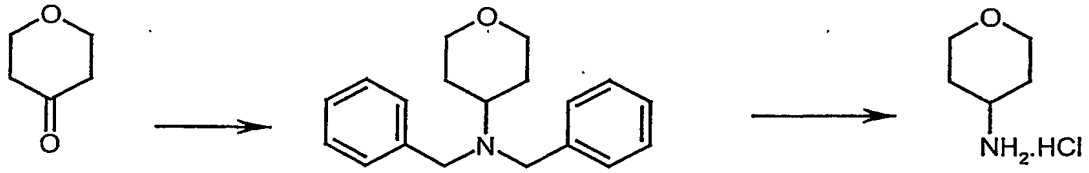


Intermediate 8: 4-Aminotetrahydropyran

Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126 (CAS 38041-19-9)



Intermediate 8A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride



Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine

Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction

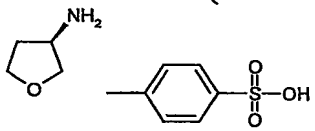
mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed $MH^+ = 282$; $T_{RET} = 1.98$ min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^1H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

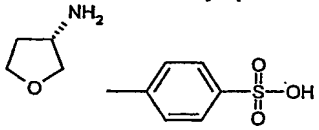
Intermediate 9: (R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate

Commercially available from Fluka Chemie AG (CAS 111769-27-8)



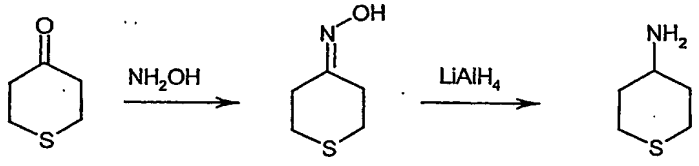
Intermediate 10: (S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate

Commercially available from E. Merck, Germany (CAS 104530-80-5)



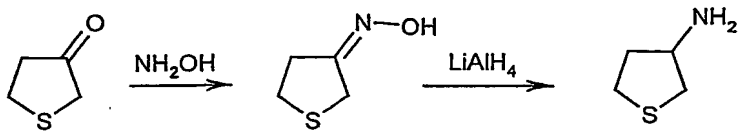
Intermediate 11: Tetrahydro-2H-thiopyran-4-amine

Prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



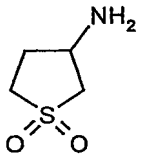
Intermediate 12: Tetrahydro-3-thiopheneamine

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



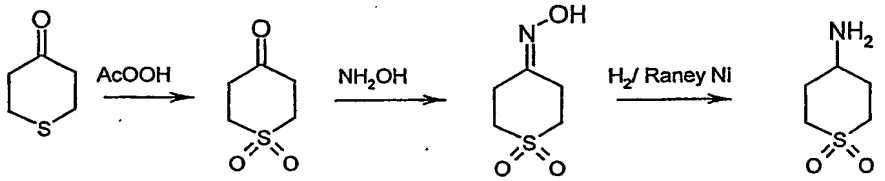
Intermediate 13: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride

Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

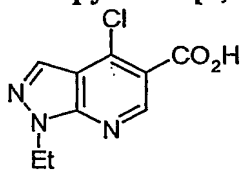


Intermediate 14: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. Oxidation to 1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.

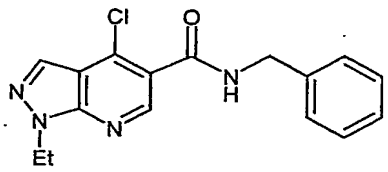


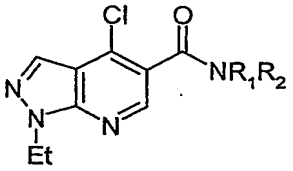
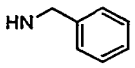
Intermediate 15: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 15 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 17: N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

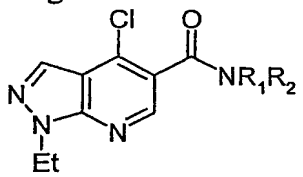


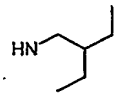
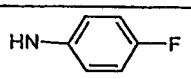
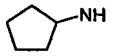
That is, Intermediate 17 is:  wherein NR_1R_2 = 

Intermediate 15 (3.5g) was dried over phosphorus pentoxide for 1h, then treated with thionyl chloride (47g). The mixture was stirred and heated at 75°C for 1.3h. Excess thionyl chloride was removed in vacuo and the residual oil azeotroped with dichloromethane (DCM) to afford **Intermediate 16**, the acid chloride derivative of Intermediate 15, as a white solid (3.3g).

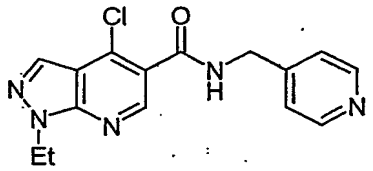
Intermediate 16 (0.473g) was dissolved in tetrahydrofuran (THF) (4ml) and treated with N,N-diisopropylethylamine (DIPEA) (0.509ml), then with benzylamine (0.209g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between dichloromethane and water. The layers were separated and the organics concentrated in vacuo to afford **Intermediate 17** (0.574g). LCMS showed MH^+ = 315; T_{RET} = 2.90min.

Similarly prepared were the following:



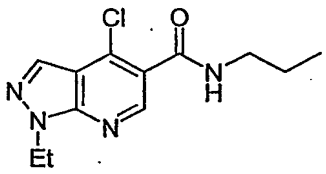
	NR1R2	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 18		2-Ethyl-N-butylamine	309	3.07
Intermediate 19		4-Fluoroaniline	319	3.08
Intermediate 20		Cyclopentylamine	293	2.76
Intermediate 21		Pyrrolidine	279	2.46

Intermediate 22: 4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



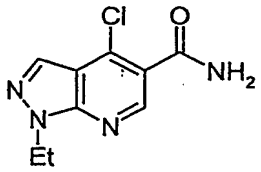
Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with diisopropylethylamine (DIPEA) (0.509ml), then with 4-(aminomethyl)pyridine (0.211g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo, then applied to an SPE cartridge (silica, 10g) which was eluted with a gradient of cyclohexane : EtOAc (2:1 increasing stepwise up to 0:1), followed by MeOH : EtOAc (5:95, then 10:90). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 22 (0.086g). LCMS showed $MH^+ = 316$; $T_{RET} = 1.84$min.

Intermediate 23: 4-Chloro-1-ethyl-N-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with DIPEA (0.509ml), then with propyl amine (0.115g) and the mixture stirred under nitrogen for 0.5h. A further portion of propyl amine (0.023g) was then added and stirring continued for 18h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo to afford Intermediate 23 (0.405g). LCMS showed $MH^+ = 267$; $T_{RET} = 2.54$min.

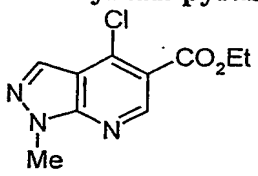
Intermediate 24: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.30g) was dissolved in THF (3ml) and treated with a 0.5M solution of ammonia in dioxane (4.92ml). The mixture was stirred under nitrogen for 18h. A further portion of 0.5M ammonia in dioxane (4.92ml)

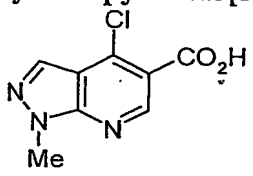
was added and stirring continued for 72h. The mixture was concentrated in vacuo and the residue partitioned between DCM and 2M sodium hydroxide solution. The layers were separated and the organics concentrated to afford Intermediate 24 (0.278g). LCMS showed $MH^+ = 225$; $T_{RET} = 2.10$min.

Intermediate 25: Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



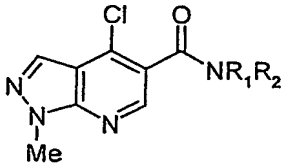
A mixture of 5-amino-1-methyl pyrazole (4.0g) and diethylethoxymethylene malonate (9.16ml) was heated at 150°C under Dean Stark conditions for 5h. Phosphorous oxychloride (55ml) was carefully added to the mixture and the resulting solution heated at 130°C under reflux for 18h. The mixture was concentrated in vacuo, then the residual oil cooled in an ice bath and treated carefully with water (100ml)(caution: exotherm). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The residual solid was purified by Biotage chromatography (silica, 90g), eluting with Et_20 : petrol (1:3). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 25 (4.82g). LCMS showed $MH^+ = 240$; $T_{RET} = 2.98$min

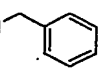
Intermediate 26: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 25 (4.0g) in dioxane (30ml) was treated with potassium hydroxide (7.54g) as a solution in water (20ml). The mixture was stirred for 16h, then diluted with water (150ml) and acidified to pH 3 with 5M aqueous hydrochloric acid. The mixture was stirred in an ice bath for 15min, then collected by filtration, washed with ice-cold water and dried in vacuo over phosphorous pentoxide to afford Intermediate 26 as a white solid (2.83g). LCMS showed $MH^+ = 212$; $T_{RET} = 2.26$min.

Intermediate 28: N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

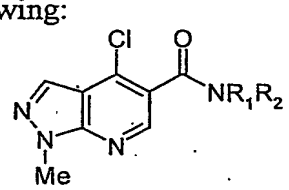


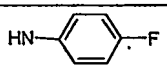
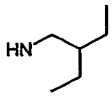
Intermediate 28 NR_1R_2 = 

Intermediate 26 (2.5g) (previously dried over phosphorus pentoxide) was treated with thionyl chloride (25ml) and the mixture heated under reflux for 1h. Excess thionyl chloride was removed in vacuo to afford **Intermediate 27**, the acid chloride derivative of Intermediate 26, as a white solid (2.7g).

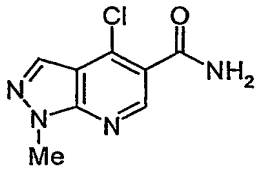
Intermediate 27 (0.68g) was dissolved in THF (10ml) and treated with DIPEA (0.77ml), then with benzyl amine (0.339g) and the mixture stirred under nitrogen for 3h. The mixture was concentrated in vacuo, then partitioned between DCM (20ml) and water (10ml). The layers were separated and the organics concentrated in vacuo to afford **Intermediate 28** (0.90g). LCMS showed $MH^+ = 301$; $T_{RET} = 2.72$min.

Similarly prepared were the following:



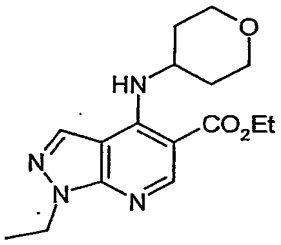
	NR1R2	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 29		4-Fluoroaniline	305	2.91
Intermediate 30		2-Ethyl-N-butylamine	295	2.97

Intermediate 31: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



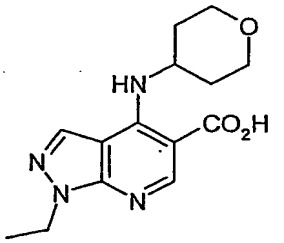
Acid chloride Intermediate 27 was synthesised from Intermediate 26 using the method shown above for Intermediate 28. Intermediate 27 (0.68g) was then treated with a 0.5M solution of ammonia in dioxane (17.7ml). Diisopropylethylamine (0.51ml) was then added and the mixture stirred for 21h. The mixture was then partitioned between DCM (100ml) and water (30ml). An insoluble solid was removed by filtration, washed with water (20ml) and dried in vacuo over phosphorous pentoxide to afford Intermediate 31 (0.544g). LCMS showed $MH^+ = 211$; $T_{RET} = 1.84$min.

Intermediate 32 (= Example 3): Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



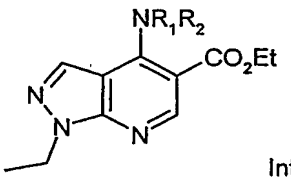
Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (0.088g) was added. The mixture was stirred under nitrogen, heated at 80°C for 16h, then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 32 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

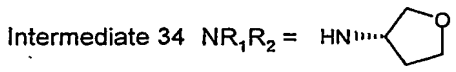
Intermediate 33: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 32 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50°C for 8h, then concentrated in vacuo, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 33 as an off-white solid (0.156g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

Intermediate 34: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

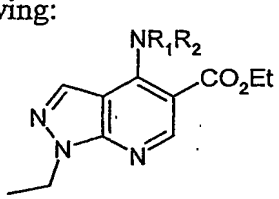


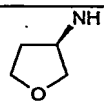
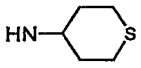
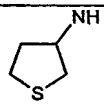
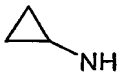
Intermediate 34 NR_1R_2 = 

Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluenesulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature,

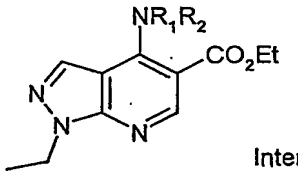
ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 34 (0.052g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.70$min.

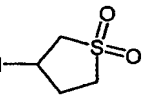
Similarly prepared were the following:



	NR_1R_2	Amine Reagent	MH^+ ion	T_{RET}(min)
Intermediate 35		(R)-(+)-3-Aminotetrahydrofuran 4-toluenesulphonate	305	2.73
Intermediate 36		Intermediate 11	335	3.21
Intermediate 37		Intermediate 12	321	3.10
Intermediate 38		Cyclopropylamine	275	2.98

<u>Intermediate 39:</u> Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

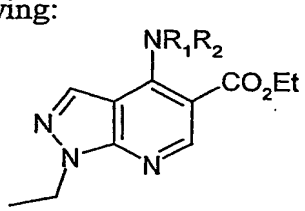


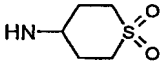
Intermediate 39 NR_1R_2 = 

Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of

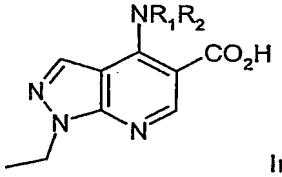
EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 39 (0.045g) as a mixture of enantiomers. LCMS showed $MH^+ = 353$; $T_{RET} = 2.60$min.

Similarly prepared was the following:



	NR_1R_2	Amine Reagent	MH^+ ion	T_{RET}(min)
Intermediate 40		Intermediate 14	367	2.64

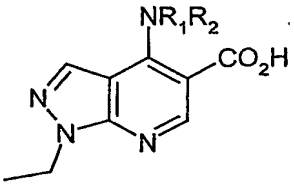
Intermediate 41: 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



Intermediate 41 NR_1R_2 = 

A solution of Intermediate 34 (0.037g) in ethanol : water (95:5, 3ml) was treated with sodium hydroxide (0.019g). The mixture was heated at 50°C for 16h, then concentrated in vacuo. The residue was dissolved in water (1.5ml) and acidified to pH 4 with acetic acid. The resultant white solid precipitate was removed by filtration and dried under vacuum. The filtrate was extracted with ethyl acetate and the organic layer collected and concentrated in vacuo to afford a further portion of white solid. The two solids were combined to afford Intermediate 41 (0.033g). LCMS showed $MH^+ = 277$; $T_{RET} = 2.05$ min.

Similarly prepared were the following:



	NR_1R_2	Starting material	MH^+ ion	T_{RET}(min)

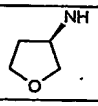
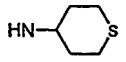
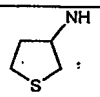
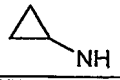
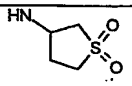
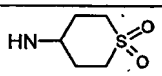
Intermediate 42		Intermediate 35	277	2.05
Intermediate 43		Intermediate 36	307	2.40
Intermediate 44		Intermediate 37	293	2.59
Intermediate 45		Intermediate 38	247	2.24
Intermediate 46		Intermediate 39	325	2.05
Intermediate 47		Intermediate 40	339	2.05

Table of Examples

Example Number	Name
1	Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
4	Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
6	Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
7	Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
8	Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
9	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
10	Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
11	Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-

	carboxylate
12	Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
13	Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
14	Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
15	Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
16	Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
17	Ethyl 4-(cyclopentylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
18	Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
19	Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
20	Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
21	N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
22	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
23	N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
24	4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
25	N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
26	N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
27	4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
28	N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine
29	N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine
30	1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
31	4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
32	4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
33	1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

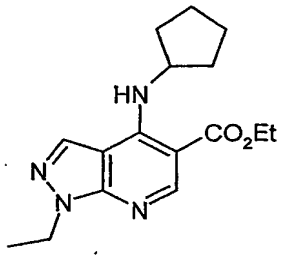
34	4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
35	4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
36	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
37	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
38	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
39	N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
40	N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
41	4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
42	4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
43	4-(Cyclohexylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
44	1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
45	1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
46	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
47	4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
48	4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
49	1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
50	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
51	4-(Cyclopentylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
52	4-(Cyclohexylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
53	1-Ethyl-N-n-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
54	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
55	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-

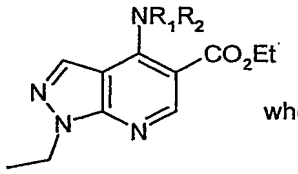
	b]pyridine-5-carboxamide
56	N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
57	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
58	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
59	N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
60	4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
61	N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
62	N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
63	N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
64	4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
65	4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
66	N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
67	4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
68	4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
69	N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
70	4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
71	4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
72	1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
73	N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
74	4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
75	N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
76	4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

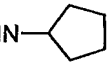
77	N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
78	4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
79	1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
80	4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
81	1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
82	1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
83	1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
84	1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
85	N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
86	N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
87	N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
88	N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
89	N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
90	N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
91	N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
92	1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
93	1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
94	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
95	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
96	4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
97	4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-

	pyrazolo[3,4-b]pyridine-5-carboxamide
98	4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

Example 1: Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

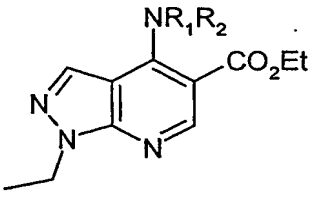


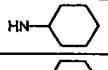
That is, Example 1 is 

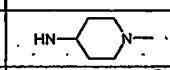
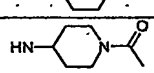
where NR_1R_2 = 

Intermediate 1 (0.051g) and cyclopentyl amine (0.019g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was loaded directly onto an solid phase extraction (SPE) cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc, (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Example 1 (0.074g). LCMS showed $MH^+ = 303$; $T_{RET} = 3.45$min.

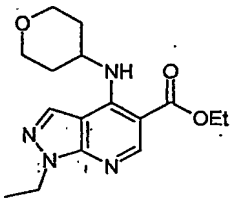
Similarly prepared were the following:



	NR_1R_2	Amine reagent	MH^+ ion	T_{RET}(min)
Example 2		Cyclohexyl amine	317	3.65
Example 3		4-Amino	319	2.93

		tetrahydropyran		
Example 4		Intermediate 7	332	2.17
Example 5		Intermediate 6	360	3.20

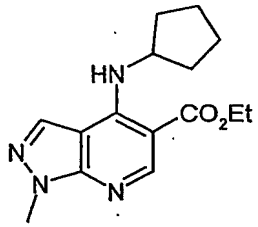
<u>Example 3</u> (=Intermediate 32): Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Instead of the method shown above (called Method A), the compound of Example 3 can also be made using the following method:

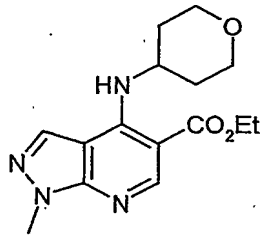
Example 3, Method B: Intermediate 1 (2.5g) was dissolved in acetonitrile (15ml). 4-Aminotetrahydropyran hydrochloride (1.1g) and N,N-diisopropylethylamine (9.4ml) were added and the mixture stirred under nitrogen at 85°C for 16h. A trace of starting material remained, so an additional portion of 4-aminotetrahydropyran hydrochloride (0.11g) was added and stirring continued at 85°C for a further 16h. The mixture was then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was washed with further water (2x20ml) then dried (Na_2SO_4) and concentrated in vacuo. The residue was further purified by chromatography using Biotage (silica, 90g), eluting with cyclohexane : ethyl acetate to afford Example 21 (2.45g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.90$min.

<u>Example 6:</u> Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



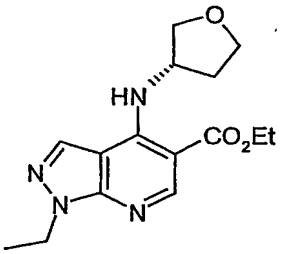
Intermediate 3 (0.045g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.07ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was evaporated to a brown solid, which was purified by mass directed autoprep HPLC, to afford Example 6 as a white solid (0.008g). LCMS showed $MH^+ = 289$; $T_{RET} = 3.22$ min.

Example 7: Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

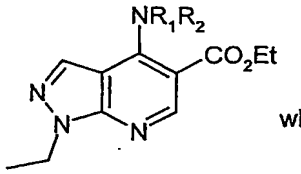


Intermediate 3 (0.035g) was placed in a Reactivial™ and treated with 4-amino tetrahydropyran (0.06ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate. The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 7 as a white solid (0.008g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.67$ min.

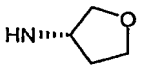
Example 8: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



that is:

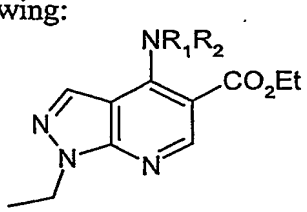


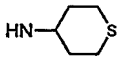
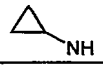
where NR_1R_2 =



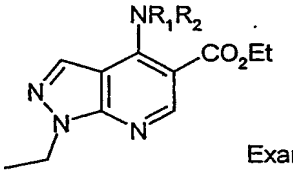
Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluene sulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 8 (0.052g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.70$min.

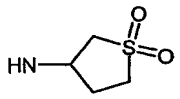
Similarly prepared were the following:



	NR_1R_2	Amine Reagent	MH^+ ion	T_{RET}(min)
Example 9		(R)-(+)-3-Aminotetrahydrofuran 4-toluene sulphonate	305	2.73
Example 10 (mixture of enantiomers)		Intermediate 11	335	3.21
Example 11 (mixture of enantiomers)		Intermediate 12	321	3.10
Example 12		Cyclopropyl amine	275	2.98

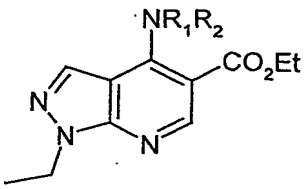
<u>Example 13:</u> Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

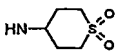


Example 13 NR_1R_2 = 

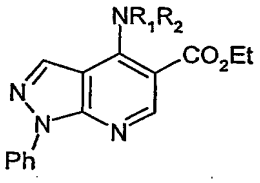
Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 13 (0.045g) as a mixture of enantiomers. LCMS showed $MH^+ = 353$; $T_{RET} = 2.60$min.

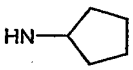
Similarly prepared was the following:



	NR_1R_2	Amine Reagent	MH^+ ion	T_{RET}(min)
Example 14		Intermediate 14	367	2.64

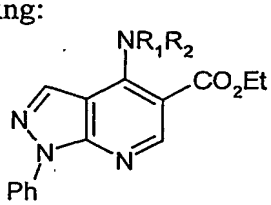
Example 15: Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

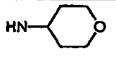


Example 15 NR_1R_2 = 

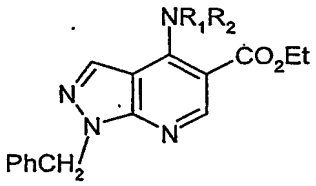
Intermediate 5 (0.02g) and cyclopentyl amine (0.007ml) were suspended in ethanol (1ml) and triethylamine (0.046ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 18h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between chloroform (1ml) and water (0.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of Et_2O : cyclohexane; (0:1 then 1:8, 1:5, 1:3, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 15 (0.024g). LCMS showed $MH^+ = 351$; $T_{RET} = 4.19$min.

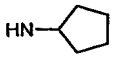
Similarly prepared was the following:



NR_1R_2	Amine Reagent	Product	MH^+ ion	T_{RET}(min)
	4-Amino tetrahydropyran	Example 16	367	3.58

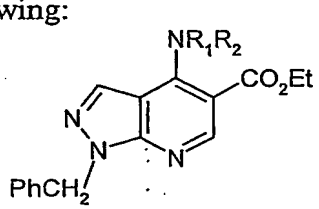
Example 17: Ethyl 4-(cyclopentylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Example 17 NR_1R_2 = 

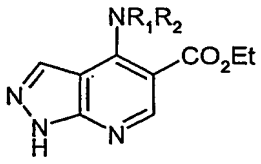
Intermediate 4 (0.04g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied as a solution in chloroform to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate : petrol (1:2). The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 17 as a white solid (0.013g). LCMS showed MH^+= 365; T_{RET} = 3.69 min.

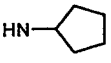
Similarly prepared was the following:



	NR_1R_2	Amine reagent	MH^+ ion	T_{RET}(min)
Example 18		4-Amino tetrahydropyran	381	3.28

Example 19: Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

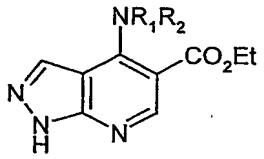


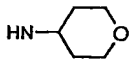
Example 19 NR_1R_2 = 

Intermediate 2 (0.035g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The residual solid was triturated with

Et_2O and the insoluble off-white solid collected and air-dried to afford Example 19 (0.016g). LCMS showed $MH^+ = 275$; $T_{RET} = 2.58$ min.

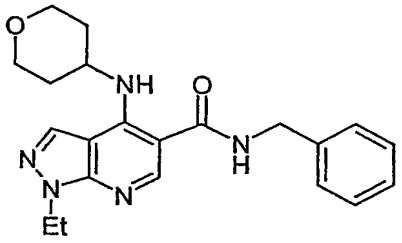
Example 20: Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

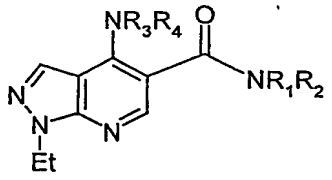


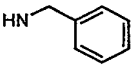
Example 20 NR_1R_2 = 

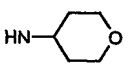
Intermediate 2 (0.035g) was placed in a Reactivial™ and treated with 4-aminotetrahydropyran (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The crude product was purified by mass directed autoprep HPLC to afford Example 20 as an off-white solid (0.011g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.08$ min.

Example 21: N-benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 21 is: 

wherein NR_1R_2 = 

NR_3R_4 = 

Three alternative methods, A, B and C, have been used to make Example 21, as follows:

Example 21, Method A:

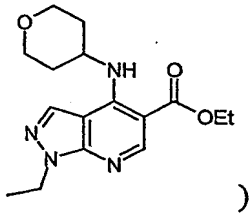
A solution of the 4-chloro Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1.9ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of 4-aminotetrahydropyran (Intermediate 8, 1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of 4-amino-

tetrahydropyran (0.01ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in dichloromethane (DCM), then applied to an solid phase extraction (SPE) cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were concentrated in vacuo to afford Example 21 (0.004g). LCMS showed $MH^+ = 380$; $T_{RET} = 2.92$min.

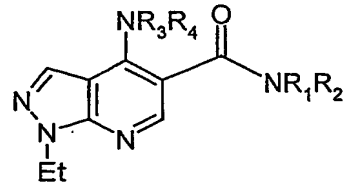
Example 21 , Method B:

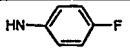
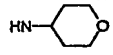
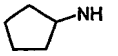
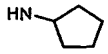
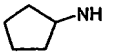
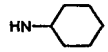
Intermediate 17 (0.031g, 0.1 mmol) was dissolved in acetonitrile (1ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 8A, 0.015g, 0.11 mmol) and N,N-diisopropylethylamine (0.08ml, 0.5 mmol) were added and the mixture stirred under nitrogen at 85°C for 16h, then concentrated in vacuo. The residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was concentrated in vacuo to afford Example 21 (0.027g). LCMS showed $MH^+ = 380$; $T_{RET} = 2.92$ min.

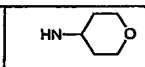
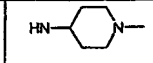
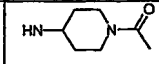
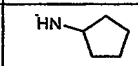
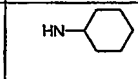
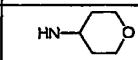
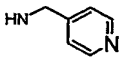
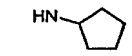
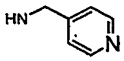
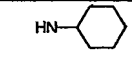
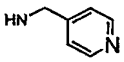
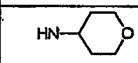
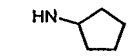
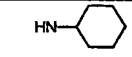
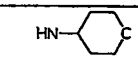
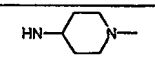
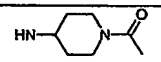
Example 21 , Method C:

This alternative route C to Example 21 involves formation of the ester of Example 3 = Intermediate 32 () using one of the methods described above, conversion of the ester of Example 3 / Intermediate 32 into the carboxylic acid (Intermediate 33) using the method given above for Intermediate 33, and then amide bond formation to form Example 21 using the method of Examples 81-84 below.

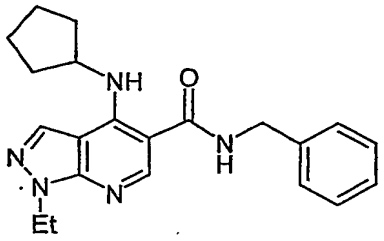
The following compounds can be similarly prepared using one or more of Methods A, B or C above, preferably Method A or B:



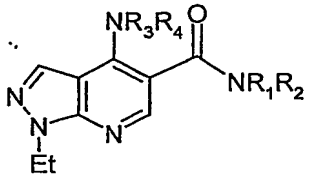
	NR1R2	NR3R4	Starting Material	Amine Reagent	MH^+ ion	T_{RET} (min)
Example 22			Intermediate 19	4-amino tetrahydropyran	384	3.09
Example 23			Intermediate 20	Cyclopentyl amine	342	3.29
Example 24			Intermediate 20	Cyclohexyl amine	356	3.47

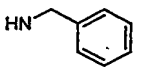
Example 25			Intermediate 20	4-amino tetrahydropyran	358	2.79
Example 26			Intermediate 20	Intermediate 7	371	2.16
Example 27			Intermediate 20	Intermediate 6	400	2.64
Example 28			Intermediate 21	Cyclopentyl amine	328	2.69
Example 29			Intermediate 21	Cyclohexyl amine	342	2.87
Example 30			Intermediate 21	4-amino tetrahydropyran	344	2.33
Example 31			Intermediate 22	Cyclopentyl amine	365	2.38
Example 32			Intermediate 22	Cyclohexyl amine	379	2.54
Example 33			Intermediate 22	4-amino tetrahydropyran	381	2.09
Example 34	NH_2		Intermediate 24	Cyclopentyl amine	274	2.59
Example 35	NH_2		Intermediate 24	Cyclohexyl amine	288	2.79
Example 36	NH_2		Intermediate 24	4-amino tetrahydropyran	290	2.22
Example 37	NH_2		Intermediate 24	Intermediate 7	303	1.81
Example 38	NH_2		Intermediate 24	Intermediate 6	332	2.06

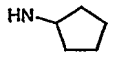
<u>Example 39:</u> N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 39 is:

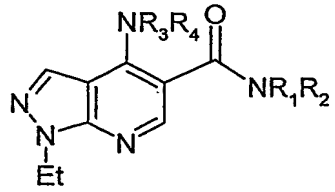


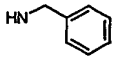
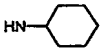
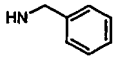
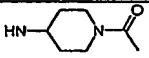
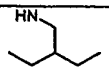
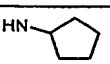
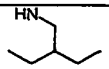
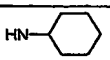
wherein NR_1R_2 = 

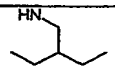
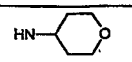
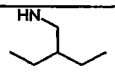
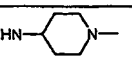
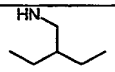
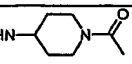
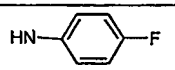
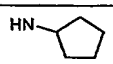
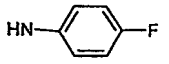
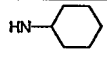
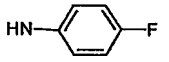
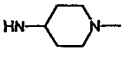
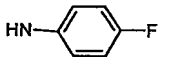
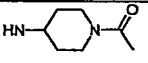
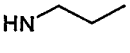
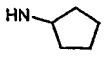
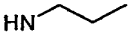
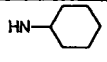
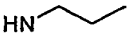
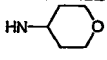
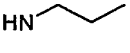
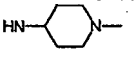
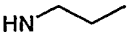
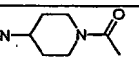
NR_3R_4 = 

A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of cyclopentyl amine (0.009ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et_2O, (iii) EtOAc and (iv) MeOH. Fractions containing desired material were combined to afford Example 39 (0.007g). LCMS showed $MH^+ = 364$; $T_{RET} = 3.38$min.

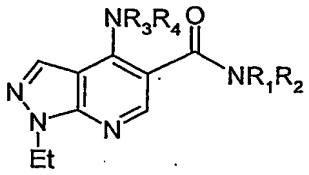
Similarly prepared were the following:

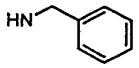


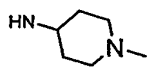
	NR1R2	NR3R4	Starting Material	Amine reagent	MH^+ ion	T_{RET} (min)
Example 40			Intermediate 17	Cyclohexyl amine	378	3.43
Example 41			Intermediate 17	Intermediate 6	422	2.75
Example 42			Intermediate 18	Cyclopentyl amine	358	3.63
Example 43			Intermediate 18	Cyclohexyl amine	372	3.79

Example 44			Intermediate 18	4-amino tetrahydro-pyran	374	3.13
Example 45			Intermediate 18	Intermediate 7	387	2.37
Example 46			Intermediate 18	Intermediate 6	416	2.92
Example 47			Intermediate 19	Cyclopentyl amine	368	3.61
Example 48			Intermediate 19	Cyclohexyl amine	382	3.76
Example 49			Intermediate 19	Intermediate 7	397	2.29
Example 50			Intermediate 19	Intermediate 6	426	2.88
Example 51			Intermediate 23	Cyclopentyl amine	316	3.05
Example 52			Intermediate 23	Cyclohexyl amine	330	3.26
Example 53			Intermediate 23	4-amino tetrahydro-pyran	332	2.58
Example 54			Intermediate 23	Intermediate 7	345	1.94
Example 55			Intermediate 23	Intermediate 6	374	2.46

<u>Example 56:</u> N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



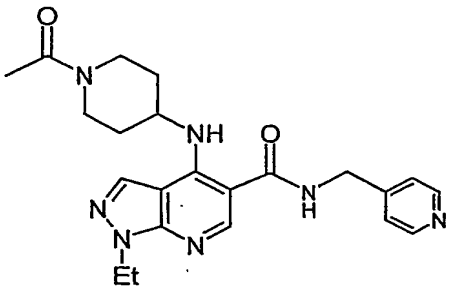
Example 56 NR_1R_2 = 

NR_3R_4 = 

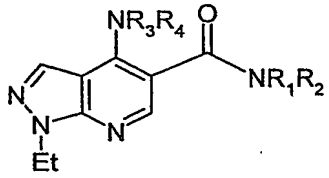
A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 7 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion Intermediate 7 (0.01ml of undiluted amine) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with

DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et_2O, (iii) EtOAc and (iv) MeOH. The methanol fraction was concentrated and further purified by SPE (silica, 0.5g) eluting with (I) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 56 (0.004g). LCMS showed $MH^+ = 393$; $T_{RET} = 2.26$min.

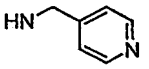
Example 57: 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



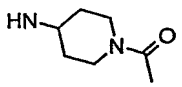
that is, Example 57 is:



wherein NR_1R_2 =



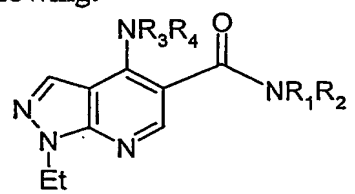
NR_3R_4 =



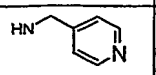
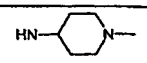
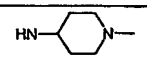
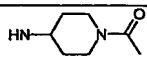
A solution of Intermediate 22 (0.03g, *ca.* 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 6 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of Intermediate 6 (0.01ml, undiluted) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol.

The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) eluting with (I) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 57 (0.003g). LCMS showed $MH^+ = 423$; $T_{RET} = 2.1$min.

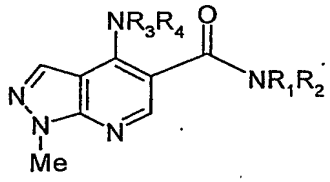
Similarly prepared were the following:

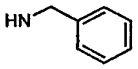


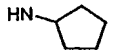
	NR1R2	NR3R4	Starting	Amine	MH^+	T_{RET}

			Material	reagent	ion	(min)
Example 58			Intermediate 22	Intermediate 7	394	1.66
Example 59			Intermediate 21	Intermediate 7	387	1.94
Example 60			Intermediate 21	Intermediate 6	386	2.3

<u>Example 61:</u> N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

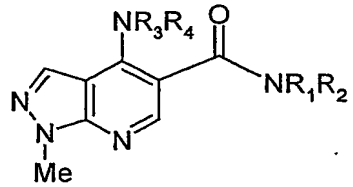


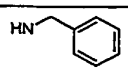
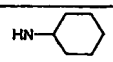
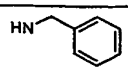
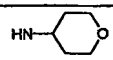
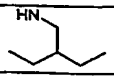
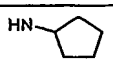
Example 61 NR_1R_2 = 

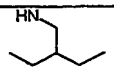
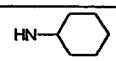
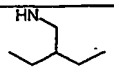
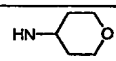
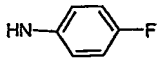
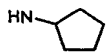
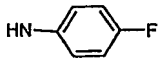
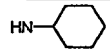
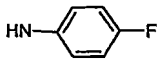
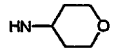
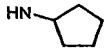
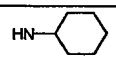
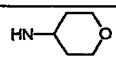
NR_3R_4 = 

A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of cyclopentyl amine (0.009ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were combined to afford Example 61 (0.039g). LCMS showed $MH^+ = 350$; $T_{RET} = 2.88$min.

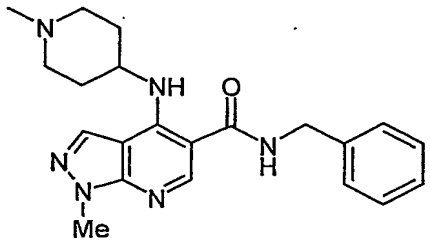
Similarly prepared were the following:



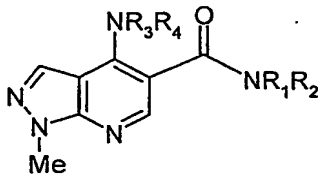
	NR1R2	NR3R4	Starting Material	Amine Reagent	MH+ ion	T_{RET} (min)
Example 62			Intermediate 28	Cyclohexyl amine	364	3.05
Example 63			Intermediate 28	4-amino tetrahydropyran	366	2.52
Example 64			Intermediate 29	Cyclopentyl	344	3.06

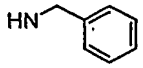
				amine		
Example 65			Intermediate 29	Cyclohexyl amine	358	3.23
Example 66			Intermediate 29	4-amino tetrahydropyran	360	2.69
Example 67			Intermediate 30	Cyclopentyl amine	354	3.17
Example 68			Intermediate 30	Cyclohexyl amine	368	3.33
Example 69			Intermediate 30	4-amino tetrahydropyran	370	2.72
Example 70	NH_2		Intermediate 31	Cyclopentyl amine	260	2.10
Example 71	NH_2		Intermediate 31	Cyclohexyl amine	274	2.29
Example 72	NH_2		Intermediate 31	4-amino tetrahydropyran	276	1.86

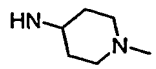
Example 73: N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 73 is:



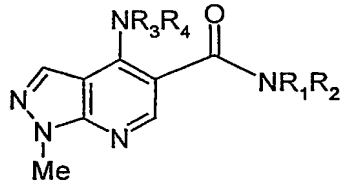
wherein NR_1R_2 = 

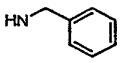
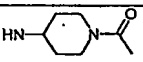
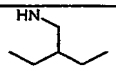
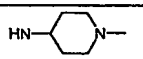
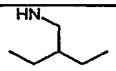
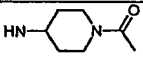
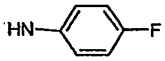
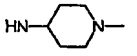
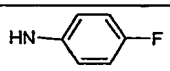
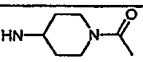
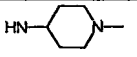
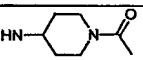
NR_3R_4 = 

A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of Intermediate 7 (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of Intermediate 7 (0.01ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by

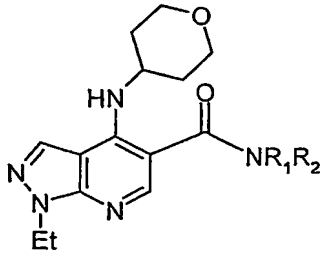
filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were combined and concentrated in vacuo. The residue was further purified by SPE (silica, 0.5g) eluting with (i) DCM, (ii) chloroform, (iii) EtOAc and (iv) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 73 (0.029g). LCMS showed $MH^+ = 379$; $T_{RET} = 2.05$min.

Similarly prepared were the following:



	NR1R2	NR3R4	Starting Material	Amine Reagent	MH+ ion	T_{RET} (min)
Example 74			Intermediate 28	Intermediate 6	407	2.57
Example 75			Intermediate 29	Intermediate 7	373	2.20
Example 76			Intermediate 29	Intermediate 6	401	2.74
Example 77			Intermediate 30	Intermediate 7	383	2.12
Example 78			Intermediate 30	Intermediate 6	411	2.69
Example 79	NH_2		Intermediate 31	Intermediate 7	289	1.64
Example 80	NH_2		Intermediate 31	Intermediate 6	317	1.99

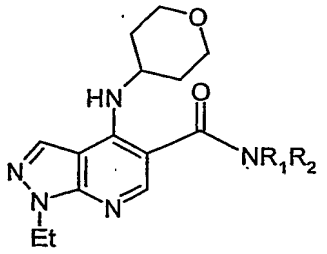
<u>Example 81</u>: 1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



Example 81 NR_1R_2 = NHMe

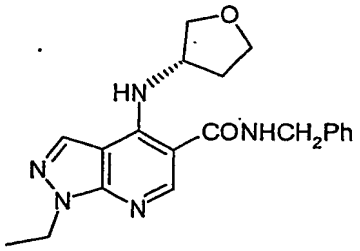
To a stirred suspension of Intermediate 33 (0.025g, ca. 0.08 to 0.09 mmol) in chloroform (2ml) was added thionyl chloride (0.025ml) and the mixture stirred at room temperature for 1h. The mixture was cooled to 0°C and methylamine added (2M solution in THF, 0.69ml = 1.38 mmol). After returning to room temperature the mixture was stirred for a further 1h, then quenched by addition of water (4ml) and the layers separated. The organic layer was concentrated then applied to an SPE cartridge (silica, 1g) which was eluted with (i) DCM, (ii) Et_2O (2:1), (iii) EtOAc, (iv) MeOH: EtOAc (1:9). Fractions containing desired material were combined to afford Example 81 (0.019g). LCMS showed $MH^+ = 304$; $T_{RET} = 2.19$min.

Similarly prepared:

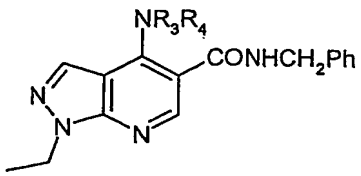


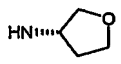
	NR1R2	Amine reagent	MH^+ ion	T_{RET} (min)
Example 82	NMe_2	Dimethylamine (2M in THF)	318	2.06
Example 83	NHEt	Ethylamine (2M in THF)	318	2.31
Example 84	NH^iPr	Isopropylamine (2M in THF)	332	2.44

Example 85: N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



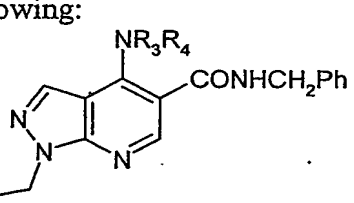
That is, Example 85 is:

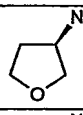
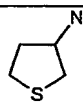
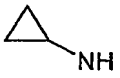
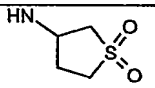
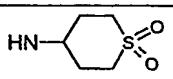


wherein NR_3R_4 = 

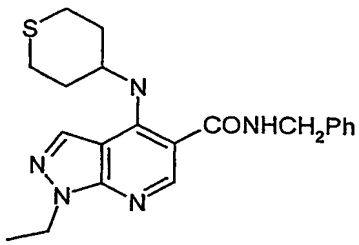
Intermediate 41 (0.017g, 0.062 mmol) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for 10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer was applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1, 2:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 85 (0.017g). LCMS showed $MH^+ = 366$; $T_{RET} = 2.80$min.

Similarly prepared were the following:



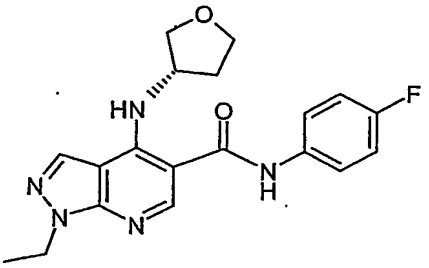
	NR_3R_4	Starting material	MH^+ ion	T_{RET} (min)
Example 86		Intermediate 42	366	2.80
Example 87		Intermediate 44	382	3.11
Example 88		Intermediate 45	336	3.00
Example 89		Intermediate 46	414	2.69
Example 90		Intermediate 47	428	2.75

Example 91: N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

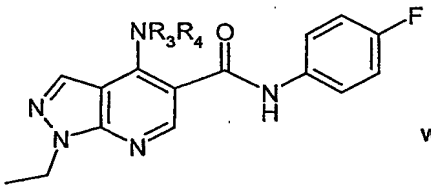


Intermediate 43 (0.019g) was dissolved in DMF (2ml), then treated with HATU (0.024g) followed by diisopropylethyl amine (0.022ml) and the mixture stirred for 10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 91 (0.023g). LCMS showed $MH^+ = 396$; $T_{RET} = 3.26$min.

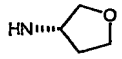
Example 92: 1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 92 is:

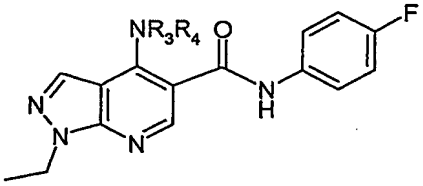


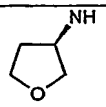
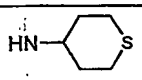
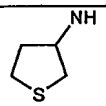
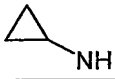
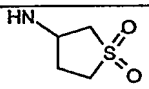
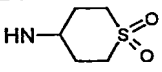
wherein NR_3R_4 =



Intermediate 41 (0.017g) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for 10 min. 4-Fluoroaniline (0.006ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer concentrated in vacuo. The crude mixture was purified by mass directed autoprep HPLC to afford Example 92 (0.013g). LCMS showed $MH^+ = 370$; $T_{RET} = 2.91$min.

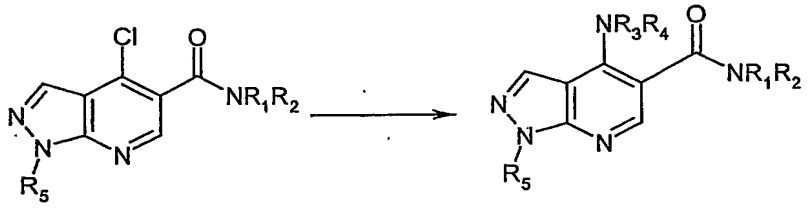
Similarly prepared were the following:



	NR_3R_4	Starting material	MH^+ ion	T_{RET} (min)
Example 93		Intermediate 42	370	2.91
Example 94		Intermediate 43	400	3.37
Example 95		Intermediate 44	386	3.27
Example 96		Intermediate 45	340	3.21
Example 97		Intermediate 46	418	2.80
Example 98		Intermediate 47	432	2.84

Example 99

In all of Examples 22 to 98, where a 4-amino 5-carboxamide Example of the following Formula I has been synthesised from the 4-chloro derivative, then an alternative final-step synthesis is as follows:



Formula IV

Formula I

An intermediate of Formula IV above (0.1mmol) was dissolved in acetonitrile (1ml). An amine of formula HR_3R_4 (0.11mmol, preferably wherein one of R_4 and R_3 = H) and N,N-diisopropylethylamine (0.5mmol) were added and the mixture stirred under nitrogen at 85°C for 16h. After concentration in vacuo, the residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was concentrated in vacuo to afford an Example of Formula I.